

Drugs in the young - part 1

Hall, M., & Hanna, L-A. (2016). Drugs in the young - part 1. *Chemist & Druggist*.

Published in:
Chemist & Druggist

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights
© 2016 C+D

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Medicine in the Young (Part 1)

Maurice Hall and Lezley-Anne Hanna

Lecturer (Education) and Senior Lecturer (Education), respectively; Queen's University Belfast

After completing this part of the module you will:

- know about the various stages of development, from birth through to adolescent (including the key terms and accepted ages)
- appreciate pharmacokinetic changes that occur in neonates
- appreciate pharmacokinetic changes that occur in infants
- appreciate pharmacokinetic changes that occur in children

Introduction

The aim of this article (Part 1) is to outline the important pharmacokinetic characteristics in the developing child that need to be accounted for when using medicines in children. Having a fundamental knowledge of these pharmacokinetic factors is important in ensuring that medicines are used safely and effectively. In the next article (Part 2), we will focus specifically on the use of medicines in children, looking particularly at factors pharmacists should consider when providing over-the-counter medicines for use in children.

The use of medicines in the young covers the time from birth through to when the development into an adult is complete. There are various stages defined in medical literature, with the following terms and ages being generally accepted:

- | | |
|---------------------|--------------------------------------------------------|
| • Preterm neonate | Born at < 37 weeks gestation |
| • Term neonate | Born at 37 to 42 weeks gestation |
| • Post-term neonate | Born at ≥42 weeks gestation |
| • Neonate | From 0 up to 28 days of age (or first 4 weeks of life) |
| • Infant | From 28 days up to 24 months of age |
| • Child | From 2 years up to 12 years of age |
| • Adolescent | From 12 years up to 18 years of age |

Key Pharmacokinetic Differences

For neonates, infants and children in particular, their stage of development is critical to how they are treated.

Absorption

Neonates

Oral delivery of drugs is unreliable due to various factors, including poor stomach emptying, higher pH environment in the stomach and differences in enzymes in the intestinal wall that metabolise drugs. This makes intravenous delivery the preferred route for most drugs. Other routes include:

- Rectal. May lead to slow and unpredictable absorption. Can be used for simple pain relief (for example, paracetamol suppositories) or treatment of seizures (for example, diazepam rectal tubes)
- Intramuscularly (for example, vitamin K or naloxone). Rate and extent of absorption is dependent on blood flow to the muscle. May cause muscle damage in premature neonates if the volume administered is too high
- Buccal (for example, glucose gel for hypoglycaemia)
- via the trachea (for example, surfactants or caffeine to aid breathing)
- Transdermal. While not commonly used, it should be noted that preterm neonates of 28 weeks' gestation or less have very thin stratum corneum and hence substances in contact with their skin could potentially be highly absorbed.

Infants and children

Oral absorption of drugs is affected by factors such as the gastric and intestinal pH and intestinal transit time. Gastric emptying approaches adult values from about 6 months of age, with gastric acid secretion becoming comparable with adult values in the second year of life. Generally, the rate at which drugs are absorbed is expected to be slower in young infants (up to around 6 months of age) than in older children. Other routes of administration which have age considerations are:

- Intramuscular – absorption is much faster than in the neonate due to increased blood flow
- Transdermal – greater perfusion and hydration of the skin, relative to adults, can influence absorption
- Rectal – a greater number of rectal contraction in infants may lead to greater likelihood of doses being ejected before absorption can occur

Distribution

Neonates and infants

For those born preterm, the neonatal period may extend to several months, with those born more than 10 weeks early or having intra-uterine growth retardation having little body fat. Conversely, where the mother has diabetes, the neonate may be larger than normal with greater levels of fat than normal. This has direct relevance to the partitioning of drug into body compartments as a consequence of its physiochemical characteristics for example, hydrophilicity or lipophilicity.

Changes in body composition during the first year of life are the most dramatic. Compared with adults, neonates and infants have large extracellular fluid and total body water spaces, which means that drugs that distribute into these spaces (for example, aminoglycosides) have a lower plasma

concentration for an equivalent dose per kg. In other words, for these medicines, higher doses of such medicines are needed to achieve the same plasma concentration.

Plasma proteins are also different in both composition and quantity in neonates and young infants. A number of factors, including lower albumin and total plasma protein levels lead to a generally higher free fraction of protein-bound drugs. This means that for drugs such as phenytoin, phenobarbital and furosemide, lower plasma concentrations may be required to achieve the same therapeutic effect as in adult patients. Additionally, neonates may have a functionally incomplete blood-brain barrier, which may result in greater levels of drug reaching the central nervous system.

Children

Differences in the distribution of drugs between children and adults are of less significance, with any variation normally being less important than the potential effect of the disease state itself on the distribution process.

Metabolism

Drug metabolism can be divided into phase 1 and phase 2 reactions; phase 1 being primarily concerned with making the drug more polar and amenable to being conjugated to a water-soluble group in phase 2. This second phase normally leads to an inactive compound that can be excreted from the body. Most of these reactions occur in the liver, with phase 1 reactions using enzymes in the cytochrome P450 (CYP) family.

Neonates and infants

The level of enzymes involved in drug metabolism are either negligible or much reduced in a neonate at term, compared with adult values. Changes in the expression of CYP enzymes occur from birth, with half-lives of drugs metabolised by these enzymes rapidly falling in response to increased expression. For example, the half-life of phenytoin has been reported to decrease from 75 hours for a preterm neonate at birth, to 24-48 hours for term neonates and then to 8 hours by 14 days after birth. Similarly, theophylline has been shown to decrease in a linear fashion with postnatal age, with a half-life reduction from 8-18 hours in term neonates, to 3-4 hours at 48 weeks' postnatal age.

Differences in metabolism are not solely confined to phase 1 reactions; several phase 2 reactions are also age-dependent. The best known of these is how neonates and young infants handle paracetamol, with conjugation reactions differing from adults in that sulfate, and not glucuronide, is the predominant group conjugated. This compensatory pathway means the half-life of paracetamol appears normal in neonates, even though they are unable to use glucuronide in their paracetamol metabolism to the same extent as adults.

Overall, the rate of metabolism is often dependent on age, with dose adjustments being necessary to deliver the same therapeutic outcome as metabolic systems develop.

Children

Older infants and young children metabolism may be higher than in adults, leading to potentially higher doses needed on a mg per kg basis. For example, one enzyme (CYP3A4), that is involved in the metabolism of a number of drugs, including carbamazepine, is known to show greater activity in children before gradually moving to adult values during adolescence. Other studies have shown the need for greater theophylline doses at in older infants and children, compared with older adolescents and adults, due to enhanced metabolic clearance.

Excretion

Neonates and infants

The renal excretion of drugs depends on three processes: glomerular filtration, tubular secretion and tubular reabsorption. In preterm neonates, the kidney is still developing, with nephron maturation being the most important determinant of renal function at birth. When adjusted for body surface area, the glomerular filtration rate of term neonates rapidly increases from around 20 mL/min at birth, doubling in the first 2 weeks of life and approaching adult values by 3 to 5 months.

Tubular secretion and reabsorption are much slower to mature, only reaching adult values in around 15 and 24 months respectively. This may have an impact on some drugs that are actively secreted in the renal tubules, such as digoxin. In general, for drugs that are mostly cleared by the kidney, immature function results in lower excretion of drugs and hence longer half-lives in the body.

Role of the pharmacist

Pharmacists are well placed to ensure medicine use in the young is safe, effective and, as much as is possible, evidence-based. We will look in more depth at medicines use in children in the next article (Part 2). Given the vulnerable nature of children with their distinctive physiology and age-related drug handling capabilities, it is important that all healthcare professionals, including pharmacists, ensure that the benefits of any medicine are not outweighed by the risks. In order to assess this, good information is essential; hence, reference sources such as the British National Formulary for Children (BNFC) are indispensable. Where information is not readily available, for example, with unlicensed or off-label medicine use, medicines information services should be contacted to determine the appropriateness of the treatment. Other useful web addresses are provided below. It is also important that pharmacists understand how key pieces of legislation may apply during consultations involving children (such as safeguarding children and patient consent). Some useful resources have been provided below.

It is also a key part of the pharmacist's role to provide good quality information to patients or carers, such as how to use their medicines, what potential side-effects or adverse reactions may occur and what to do if doses are missed or too much is taken. An important and valuable resource in this regard is the Medicines for Children website (www.medicinesforchildren.org.uk). Medicines for Children is a partnership programme by the Royal College of Paediatrics and Child Health (RCPCH), Neonatal and Paediatric Pharmacists (NPPG) and WellChild charity, which provides quality assured information about medicines for parents or carers of children. The website contains hundreds of leaflets that can be downloaded as pdfs and also has some video content showing how to administer medicines to children. It is worth noting that links to specific leaflets are included, where available, in the "Patient and Carer Advice" section of monographs within the BNFC.

Useful resources:

- National Institute for Health and Care Excellence (NICE): <https://www.nice.org.uk/>
- NICE Clinical Knowledge Summaries (CKS): cks.nice.org.uk/
- Cochrane Library: www.cochranelibrary.com/
- electronic Medicines Compendium (eMC): <https://www.medicines.org.uk/>
- NHS Choices: www.nhs.uk/

- BNFC, available from <https://www.bnf.org/> or <https://www.evidence.nhs.uk/formulary/bnfc/current> or <https://www.medicinescomplete.com/>
- British Paediatric Surveillance Unit (BPSU): <http://www.rcpch.ac.uk/bpsu>
- UK Medicines for Children Research Network (MCRN): <http://www.priomedchild.eu/whats-going-on/networks/the-uk-medicines-for-children-research-network-mcrn/>
- Neonatal and Paediatric Pharmacists Group (NPPG): <https://www.nppg.org.uk/>
- Medicines for Children: Medicinesforchildren.org
- Focus on safeguarding children and vulnerable adults: <https://www.pharmacyregulation.org/regulate/article/focus-safeguarding-children-and-vulnerable-adults>
- Pharmaceutical Society of Northern Ireland. Professional standards and guidance for patient consent: <http://www.psn.org.uk/wp-content/uploads/2012/09/StandardsonPatientConsent-revised24FEB2016.pdf>
- General Pharmaceutical Society. Guidance on consent: https://www.pharmacyregulation.org/sites/default/files/guidance_on_consent_08.09.14.pdf

Conclusion

Many important differences exist between adults and children, particularly those in the first years of life. The developing child has important pharmacokinetic characteristics that need to be accounted for when using medicines in children. For pharmacists, knowledge of these changes is important in ensuring that medicines are used safely and effectively. In the next article, we will focus specifically on the use of medicines in children, looking particularly at factors pharmacists should consider when providing over-the-counter medicines for use in children.

References

1. Office for National Statistics (ONS). Overview of the UK population: February 2016. <http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/february2016> (accessed 1st November 2016)
2. Walker, Roger. Clinical Pharmacy and Therapeutics. Elsevier Health Sciences, 2011.
3. Costello, Ian. Paediatric drug handling. Pharmaceutical Press, 2007.
4. Lu, Hong, and Sara Rosenbaum. "Developmental pharmacokinetics in pediatric populations." The Journal of Pediatric Pharmacology and Therapeutics 19.4 (2014): 262-276.
5. Jong, Geert 'T. "Pediatric development: physiology. Enzymes, drug metabolism, pharmacokinetics and pharmacodynamics." Pediatric Formulations: A Roadmap (2014): 9-23.